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Are statins effective for simultaneously treating dyslipidemias and hypertension?

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Abstract

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are unequivocally useful for lowering cholesterol levels in patients with dyslipidemias characterized by elevations in total and/or low-density lipoprotein cholesterol. The beneficial effects of statins to lower serum cholesterol translate into significant reductions in cardiovascular morbidity and mortality. In addition to lowering cholesterol levels, statins have other biological effects relevant to cardiovascular homeostasis including anti-inflammatory actions and downregulation of angiotensin type 1 receptor expression that contribute to improvements in endothelial function and arterial compliance. Since endothelial dysfunction and reduced arterial compliance are important pathophysiological determinants of essential hypertension, these actions of statins raise the possibility that statin therapy may be useful for simultaneously treating dyslipidemias and hypertension. However, it has been unclear whether statins are effective in lowering blood pressure. This controversy stems from a variety of methodological limitations including inadequate sample size, confounding effects of antihypertensive drugs, differences in blood pressure measurement techniques, and differences in patient populations. However, based on published results from both small clinical studies and large randomized clinical trials, statins modestly lower blood pressure in patients with high, but not normal, blood pressure, regardless of cholesterol level.

Keywords

HMG-CoA reductase inhibitors; Blood pressure; Dyslipidemia; Hypertension

1. Introduction

It is important to determine whether the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) significantly lower blood pressure in patients. Statins have pleiotropic effects that go beyond lowering cholesterol levels per se. For example, statins improve endothelial-dependent vasodilation, increase bioavailability of nitric oxide, and reduce levels of endothelin-1 (potent vasoconstrictor) [1]. Statins also downregulate expression of angiotensin type 1 (AT1) receptors, decrease expression of NAD(P)H oxidase subunit

p22phox, and reduce free radical release in the vasculature [2,3]. Moreover, statins improve arterial compliance [4,5]. All of these factors help to regulate hemodynamic homeostasis. The existence of these pleiotropic actions of statins raises the possibility that statins may directly lower blood pressure in addition to lowering cholesterol levels.

Several studies report a positive correlation between blood pressure and cholesterol levels. Indirect evidence from several trials investigating cholesterol-lowering regimens suggests that lowering cholesterol may simultaneously reduce blood pressure by between 2 and 5 mmHg [6]. However, conflicting results have been reported with respect to blood pressure-lowering effects of statins in humans. First of all, direct measures of blood pressure were not recorded in some clinical trials. One potential explanation for the absence of a blood pressure-lowering effect of statins in some studies is that, as with traditional antihypertensive agents, statins may only reduce blood pressure in hypertensive individuals and not normotensive subjects. Thus, effects of statins to lower blood pressure may be difficult to detect in large studies with a high proportion of normotensive subjects. Another potential explanation is that most studies of statins were not specifically designed to evaluate blood pressure effects. Therefore, small but clinically significant, changes may have been missed [7]. Indeed, blood pressure reduction does not occur with statin treatment in hypercholesterolemic, normotensive patients [8–10]. In patients with controlled hypertension (defined by WHO criteria; systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) who are also hypercholesterolemic, four studies report no change in blood pressure levels with additional statin treatment [11–14], whereas others demonstrate that additional statin therapy led to a greater reduction in blood pressure in patients with uncontrolled hypertension [5,15–17]. The differences in study outcomes may relate to differences in sample size, confounding effects of other antihypertensive drugs, methodological limitations (blood pressure measuring techniques), or differences in baseline pathology (different cholesterol or blood pressure levels, age, etc.).

2. Animal studies

Hypercholesterolemia is associated with upregulation of expression and function of vascular AT1 receptors in aortas of hypercholesterolemic rabbits [18]. Wassmann et al. [3] characterized the effects of atorvastatin in normocholesterolemic, spontaneously hypertensive rats. These animals received atorvastatin 50 mg/kg per day, a dose that produced plasma concentrations comparable to those achieved after oral administration of common doses of atorvastatin in humans. Systolic blood pressure (SBP) was significantly decreased in atorvastatin-treated rats (184 ± 5 mmHg versus $204 \pm$ mmHg for control). Statin therapy also improved endothelial dysfunction and profoundly reduced angiotensin II-induced vasoconstriction. Atorvastatin treatment also decreased aortic AT1 receptor mRNA expression and reduced mRNA expression of the essential NAD(P)H oxidase subunit p22phox. Aortic AT1 receptor protein expression was also consistently decreased. Vascular production of reactive oxygen species was reduced in statin-treated rats. Thus, in spontaneously hypertensive rats without hypercholesterolemia, treatment with atorvastatin causes a significant reduction of SBP and a profound improvement of endothelial dysfunction mediated by a reduction of free radical release in the vasculature. The underlying mechanisms may be related to the statin-induced downregulation of AT1 receptor expression and decreased expression of the NAD(P)H oxidase subunit p22phox.

3. Clinical studies

3.1. Patients with hypertension

Four studies found no change in blood pressure levels with additional statin treatment in patients with controlled hypertension [11–14]. These studies determined the effect of pravastatin or simvastatin added to antihypertensive therapy with angiotensin converting

enzyme (ACE) inhibitors and calcium antagonists or atenolol to produce additional falls in blood pressure. There were no changes in either systolic or diastolic blood pressure (DBP) following pravastatin or simvastatin. Thus, statins do not enhance the blood pressure-lowering action of ACE inhibitors, calcium antagonists or beta blockers.

We observed similar findings [19,20]. Forty-seven hypertensive, hypercholesterolemic patients (baseline SBP and DBP were 145 and 90 mmHg) were given simvastatin 20 mg and placebo, simvastatin 20 mg and losartan 100 mg, or losartan 100 mg and placebo daily during each 2-month treatment period. Losartan alone or combined therapy significantly reduced systolic and diastolic blood pressure ($-14/-8$ and $-17/-10$ mmHg, respectively) compared with baseline. These reductions were significantly greater than those observed with simvastatin alone ($-3/-3$ mmHg). However, the addition of simvastatin did not enhance the blood pressure-lowering action of losartan (Fig. 1) [19]. Fifty patients with type 2 diabetes (38 were hypertensive; baseline SBP and DBP were 134 and 80 mmHg) were given simvastatin 20 mg and placebo, simvastatin 20 mg and ramipril 10 mg, or ramipril 10 mg and placebo daily during each 2-month treatment period. Ramipril alone or combined therapy significantly reduced blood pressure ($-8/-5$ and $-11/-5$ mmHg, respectively) when compared with baseline. These reductions were significantly greater than those observed with simvastatin alone ($+1/0$ mmHg). However, the addition of simvastatin did not enhance the blood pressure-lowering action of ramipril (Fig. 2) [20].

On the other hand, most studies (except for one [25]) demonstrate that additional statin therapy leads to a greater reduction in blood pressure in patients with uncontrolled hypertension [5, 15–17, 21–24]. Borghi et al. [15] compared the extent of blood pressure changes in 41 patients with hypertension and hypercholesterolemia, taking antihypertensive drugs and treated for 3 months with statins (HC-S; pravastatin or simvastatin) and compared with matched controls with high (HC-D; 44) or normal serum cholesterol (NC-D; 45) undergoing antihypertensive treatment combined with dietary treatment alone. After 3 months of follow-up, a greater reduction of SBP and DBP values was observed in HC-S patients ($-11.3\pm 3/-10.6\pm 2\%$) when compared with both HC-D ($-6.6\pm 2/-6.1\pm 2\%$; $p < 0.05$) and NC-D ($-6.9\pm 2/-6.8\pm 1.5\%$; $p < 0.05$). In statin-treated patients, a slight linear relation was found between the percentage changes in DBP and those in plasma total cholesterol ($R = 0.37$, $p = 0.043$), whereas no relation was found with SBP changes. This study demonstrates that the use of statins in combination with antihypertensive drugs can improve blood pressure control in patients with uncontrolled hypertension and high serum cholesterol levels. Sposito et al. [16] compared blood pressure reduction between patients receiving ACE inhibitors (enalapril or lisinopril) alone and patients receiving these medications plus statins (lovastatin or pravastatin). The statin-treated group had a greater reduction in BP and total cholesterol levels at week 16. In this study, the baseline SBP and DBP were 153 and 100 mmHg in the statins + ACE inhibitors group and 149 and 102 mmHg in the ACE inhibitors group. The baseline SBP and DBP were higher than in our study with hypertensive, hypercholesterolemic patients (baseline SBP and DBP were 145 and 90 mmHg). It is possible that differences in baseline SBP and DBP or other factors resulted in different observations regarding the absence of synergistic effect of blood pressure lowering of simvastatin combined with losartan or ramipril in our studies.

Twenty-five persons with moderate hypercholesterolemia and untreated hypertension (systolic and diastolic blood pressure 149 ± 6 and 96 ± 2 mmHg) were randomized in a double-blind manner to placebo or pravastatin (20–40 mg/day) in a crossover design. Pravastatin decreased systolic and diastolic blood pressure (-8 and -5 mmHg, both $p = 0.001$), and pulse pressure (-3 mmHg, $p = 0.011$) and blunted the blood pressure increase caused by the cold pressor test (-4 mmHg, $p = 0.005$) compared with placebo (Fig. 3). It also reduced the level of circulating endothelin-1 ($p = 0.001$). When participants were taking either placebo or pravastatin, blood pressure was not significantly correlated with total or low-density lipoprotein cholesterol or

with circulating endothelin-1 [17]. The effects of intensive cholesterol reduction on large artery stiffness and blood pressure in normolipidemic patients with isolated systolic hypertension were investigated. Twenty-two patients with stage I isolated systolic hypertension received 3 months of atorvastatin therapy (80 mg/day) and 3 months of placebo treatment. Systemic arterial compliance was higher after treatment (placebo versus atorvastatin: 0.36 ± 0.03 versus 0.43 ± 0.05 mL/mmHg, $p = 0.03$). Brachial SBP was lower after atorvastatin treatment (154 ± 3 mmHg versus 148 ± 2 mmHg, $p = 0.03$), as were mean (111 ± 2 mmHg versus 107 ± 2 mmHg, $p = 0.04$) and DBP (83 ± 1 mmHg versus 81 ± 2 mmHg, $p = 0.04$). Thus, intensive cholesterol reduction may be beneficial in the treatment of patients with isolated systolic hypertension and normal lipid levels, through a reduction in large artery stiffness [5].

Hyperlipidemic subjects with hypertension were randomized into groups to receive atorvastatin 20 mg/day or placebo for 8 weeks. The atorvastatin group ($n = 15$) had mean 24 h SBP 153.1 ± 4.8 mmHg, DBP 87.1 ± 6.7 mmHg while the placebo group ($n = 16$) had mean 24 h SBP 151.1 ± 7.4 mmHg, DBP 84.8 ± 5.9 mmHg. Twenty-four hours ambulatory BP (ABP) monitoring was performed at study entry and after 8 weeks. In the atorvastatin group there were significant reductions of SBP (13.7 ± 5.6 mmHg, $p < 0.001$), DBP (7.8 ± 5.7 mmHg, $p < 0.01$) and improvement of brachial artery flow-mediated dilation ($4.2 \pm 2.6\%$). No significant changes in blood pressure and flow-mediated dilation were observed in the placebo group [21]. In another study, 36 hypertensive and dyslipidemic patients were treated with atorvastatin 20 mg/day for 8 weeks. The ABP monitoring was carried out at study entry and at the end of 8 weeks. The ABP monitoring studies indicated significant reductions in total average SBP, total average DBP, total average mean blood pressure, day average SBP, day average DBP, night average SBP, night average DBP, and night average mean blood pressure levels in the atorvastatin group [22]. Another preliminary study demonstrated similar observations [23].

3.2. In patients without hypertension

Blood pressure reduction does not occur with statin treatment in hypercholesterolemic, normotensive patients [8–10,20,22,26–31]. In one study, patients with primary hypercholesterolemia received pravastatin 40 mg or placebo each for 8 weeks. Blood pressure was not influenced by pravastatin [9]. In another study of hypercholesterolemic patients, treatment with pravastatin 40 mg did not alter blood pressure, vascular resistance, or arterial compliance [10].

The effect of mean dose atorvastatin 16 mg was investigated on arterial compliance in hypercholesterolemic, normotensive patients. After 20 weeks of treatment, large artery elasticity index did not change significantly, but small artery elasticity index significantly increased by 21%. Both SBP and DBP decreased significantly (6 and 3 mmHg, respectively). Atorvastatin improves the elasticity of small arteries and reduces SBP and DBP in hypercholesterolemic, normotensive patients [4].

Conflicting results regarding blood pressure-lowering effects of statins may relate to methodological limitations (blood pressure measuring techniques) or to differential effects of statins in different biological conditions (cholesterol or blood pressure levels, age, etc.). Terzoli et al. [32] performed a clinical study to address the conflicting results regarding blood pressure-lowering effect of statins. Patients with cholesterol >200 mg/dL and no previous statin treatment underwent 24-h ABP monitoring and were classified as normotensives or hypertensives according to their ABP. They were randomized to statin (simvastatin or pravastatin, 10–20 mg/day; atorvastatin, 5–10 mg/day) or control treatment (soy lecithin, 20 g/day) for 2 months, after which ABP assessment was repeated. No consistent treatment-related reduction in ABP was observed in statin-treated normotensive patients (SABP -0.7 , DABP -1.0 mmHg). In contrast, statin-treated hypertensive patients showed lower SABP -5.7 and DABP -3.5 mmHg (both $p < 0.001$) and the effect was entirely accounted for by reduced

daytime values with no change in nighttime values. The treatment-related blood pressure reduction was significantly correlated to the baseline level of systolic as well as diastolic blood pressure, but not with the concomitant statin-induced cholesterol reduction. Statins moderately but significantly lower blood pressure in patients with high (but not with normal) ABP.

3.3. Large scale clinical trials

The prospective, population-based, longitudinal Brisighella Heart Study evaluated the effect of different lipid-lowering strategies on blood pressure control in subjects with hypercholesterolemia [33]. A total of 1356 subjects with total cholesterol levels ≥ 239 mg/dL were randomly treated for 5 years with one of four lipid-lowering regimens: low-fat diet, cholestyramine, gemfibrozil, or simvastatin. Participants were divided at baseline into four quartiles according to SBP level (<130 , 130–139, 140–154, >154 mmHg) and examined for the percent change in SBP and DBP during the 5 years of treatment. Significant decreases in SBP and DBP were observed in the two upper quartiles of SBP ≥ 140 mmHg and were greater in subjects treated with simvastatin than in subjects treated with low-fat diet, cholestyramine, or gemfibrozil. A subset of 533 subjects treated with antihypertensive drugs were analyzed separately to further investigate the putative role of the interactions among simvastatin, blood pressure control, and hypertension. The effects of simvastatin on blood pressure control were restricted to the two upper quartiles of SBP ≥ 140 mmHg. In particular, the average reduction in blood pressure was enhanced in subjects in the fourth quartile, whose blood pressure control was poor despite receiving antihypertensive drug therapy. Conversely, no significant changes in blood pressure were observed in subjects in the lower two quartiles, with normal baseline blood pressure values (SBP <140 mmHg). Thus, the use of statins may significantly improve blood pressure control in subjects with both hypercholesterolemia and uncontrolled hypertension. The University of California, San Diego (UCSD) Statin Study enrolled 1016 men and women with low-density lipoprotein cholesterol levels from 115 to 190 mg/dL [34]. Participants were randomized in a 1:1:1 fashion to 20 mg of simvastatin, 40 mg of pravastatin, or placebo for 6 months. At 6 months, simvastatin was associated with a 2.79 mmHg decrease in SBP and a 2.67 mmHg drop in DBP, while pravastatin led to a 2.47-mmHg decline in SBP and a 2.47-drop in DBP. All the values were statistically significant ($p < 0.0102$ for systolic, $p < 0.0024$ for diastolic). In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA) trial, at baseline and study end (mean follow-up 3.3 years), the mean blood pressure of the 10,305 patients included did not differ between those allocated atorvastatin 10 mg ($n = 5168$) and placebo ($n = 5137$). However, between 6 weeks and 18 months, those allocated statin had significantly lower blood pressure levels than those allocated placebo. Maximal differences were 1.1 mmHg systolic and 0.7 mmHg diastolic (both $p < 0.001$) (Fig. 4). Atorvastatin use was associated with a small but significant reduction in blood pressure levels until extra antihypertensive drug use in the placebo group obscured this blood pressure effect [35]. Four hundred four patients in North America and Europe were randomized in a double-blind manner to receive 12 weeks of valsartan 160 mg ($n = 135$) or valsartan 160 mg added to simvastatin 20 ($n = 131$) or 80 mg ($n = 127$). All patients underwent 24 h ABP. ABP was reduced to a similar extent in all groups with no evidence for an additive effect with simvastatin on blood pressure (Fig. 4) [13].

4. Discussion

A recent meta-analysis demonstrates that SBP was significantly lower in patients on statins than in those on placebo or control hypolipidemic drug (mean difference: -1.9 mmHg; 95% CI: -3.8 to -0.1). The effect is greater when the analysis was restricted to studies with a baseline SBP >130 mmHg (Delta SBP: -4.0 ; 95% CI: -5.8 to -2.2 mmHg). There is a trend for lower DBP in patients receiving statin therapy compared with control: -0.9 mmHg (95% CI: -2.0 to 0.2) overall and -1.2 mmHg (95% CI: -2.6 to 0.1) in studies with a baseline DBP >80 mmHg.

In general, the higher the baseline blood pressure, the greater the effect of statins on blood pressure ($p = 0.066$ for SBP and $p = 0.023$ for DBP). The blood pressure response to statins is unrelated to age, changes in serum cholesterol, or length of the trial [36].

These findings are consistent with ours. However, we observed different effects of statins between patients with uncontrolled hypertension and patients with controlled hypertension or normotension. We conclude that statins significantly lower blood pressure in the former patients, however, statins did not in the latter patients. Indeed, the meta-analysis demonstrated this in the subgroup analysis. The effect was greater when the analysis was restricted to studies with a baseline SBP >130 mmHg (Delta SBP: -4.00 ; 95% CI: -5.81 to -2.18 mmHg versus $+0.03$; 95% CI: -1.91 to 1.96 mmHg with a baseline SBP <130 mmHg). There was a trend for lower DBP in patients receiving statin therapy in studies with a baseline DBP >80 mmHg (Delta DBP: -1.24 mmHg; 95% CI: -2.57 to 0.10 versus -0.46 ; 95% CI: -1.47 to 0.56 mmHg with a baseline DBP <80 mmHg). In those trials where SBP at baseline was <130 mmHg and/or DBP <80 mmHg, the average net effect of statins on systolic and diastolic BP, respectively, was negligible.

Even this well-performed meta-analysis study demonstrated significant heterogeneity between studies (both $p < 0.01$ to SBP and DBP) because they were carried out in a variety of settings, with different methods particularly blood pressure measurement, small or very small sample size, effects of concomitant antihypertensive therapy, using various criteria and different comparative groups. These factors can greatly affect the interpretation of the results. In addition, this kind of meta-analysis has some flaws because it assembles data from secondary sources (published papers) rather than the primary data set. For example, this meta-analysis study quoted our paper [19]. It reported that simvastatin increased SBP by 5.00 mmHg and DBP by 4.00 mmHg. But in fact, simvastatin decreased SBP by 3 mmHg ($p = 0.058$) and DBP by 3 mmHg ($p = 0.052$) shown in Fig. 1. The baseline SBP and DBP were 145 and 90 mmHg. And in a different study of ours in patients with type 2 diabetes [20], simvastatin increased SBP by 1 mmHg ($p = 0.659$) and DBP by 0 mmHg ($p = 0.827$) shown in Fig. 2. The baseline SBP and DBP were 134 and 80 mmHg.

Our observations were confirmed in a large randomized controlled trial. In the Brisighella Heart Study, the effects of simvastatin on blood pressure control were restricted to the two upper quartiles of SBP ≥ 140 mmHg. In particular, the average reduction in blood pressure was enhanced in subjects in the fourth quartile, whose blood pressure control was poor despite receiving antihypertensive drug therapy. Conversely, no significant changes in blood pressure were observed in subjects in the lower two quartiles, with normal baseline blood pressure values (SBP <140 mmHg). Thus, the use of statins may significantly improve blood pressure control in subjects with both hypercholesterolemia and uncontrolled hypertension [33]. In the ASCOT-LLA trial, between 6 weeks and 18 months, patients assigned to statin treatment had significantly lower blood pressure levels than those treated with placebo. However, these differences were minimized because patients on placebo tended to receive a slightly greater number of antihypertensive study drugs at each stage of the trial and they also received a greater number of antihypertensive non-study drugs (significantly and increasingly from 1st year onwards) [35]. Similarly, another study reported that in hypertensive, hypercholesterolemic patients, valsartan controlled blood pressure in these patients. However, the addition of simvastatin to valsartan did not enhance the blood pressure-lowering action of valsartan [13].

Hypercholesterolemia and hypertension are both associated with endothelial dysfunction and their coexistence is associated with an increased incidence of cardiac events in epidemiological studies. In pigs with both hypercholesterolemia and hypertension, the vasodilator response of coronary arteries to bradykinin and calcium ionophores is significantly impaired and increased oxidative stress is observed when compared with only hypercholesterolemia or hypertension

alone. These results suggest that hypercholesterolemia and hypertension have a synergistic deleterious effect on coronary endothelial function that is associated with increased oxidative stress [37]. Angiotensin II is a potent endogenous vasoconstrictor while low-density lipoprotein induces upregulation of the AT1 receptor [38]. Indeed, hypercholesterolemic rabbits display enhanced vascular expression of AT1 receptors that mediate increased activity of angiotensin II [18]. Furthermore, the effect of statins to reverse the elevated blood pressure response to angiotensin II infusion is accompanied by downregulated AT1 receptor density [2]. Angiotensin II promotes super-oxide anion generation and endothelial dysfunction [39,40]. C-reactive protein upregulates AT1 receptors in vascular smooth muscle cells and these effects are attenuated by losartan [41]. Accordingly, combined simvastatin/ramipril or losartan therapy may have additional beneficial effects by distinct and interrelated mechanisms even though addition of simvastatin did not enhance the blood pressure-lowering action of ramipril, losartan, or valsartan. Indeed, we have observed that combined therapy significantly reduces plasma malondialdehyde, monocyte chemoattractant protein-1, and C-reactive protein levels more than monotherapy [19,20]. The additive beneficial effects of combined therapy are consistent with previous experimental [42–44] and clinical studies [45,46]. Thus, there is a scientific rationale for recommending a combination of statins and ACE inhibitors or AT1 receptor blockers to prevent atherosclerosis and coronary heart disease even in patients with controlled hypertension [47–50].

5. Summary

It has been unclear whether statins are effective in lowering blood pressure. This controversy stems from a variety of methodological limitations including inadequate sample size, confounding effects of antihypertensive drugs, differences in blood pressure measurement techniques, and differences in patient populations. However, based on published results from both small clinical studies and large randomized clinical trials, statins modestly lower blood pressure in patients with high, but not normal, blood pressure, regardless of cholesterol level (Table 1).

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Fig. 1.

Change in systolic and diastolic blood pressure at respective pretreatment baseline and after treatment with simvastatin alone, combined therapy, and losartan alone (both $p < 0.001$ by ANOVA). In 47 hypertensive, hypercholesterolemic patients, simvastatin alone reduced SBP from 145 to 142 mmHg ($p = 0.058$) and DBP from 90 to 87 mmHg ($p = 0.052$). When losartan controlled blood pressure in these patients, the addition of simvastatin on losartan did not enhance the blood pressure-lowering action of losartan [19]. SEM is identified by bars.

Fig. 2.

Change in systolic and diastolic blood pressure at respective pretreatment baseline and after treatment with simvastatin alone, combined therapy, and ramipril alone (both $p < 0.001$ by ANOVA). In 50 patients with type 2 diabetes (38 were hypertensive), simvastatin alone did not reduce SBP from 134 to 135 mmHg ($p = 0.659$) and DBP from 80 to 80 mmHg ($p = 0.827$). When ramipril controlled blood pressure in these patients, the addition of simvastatin on ramipril did not enhance the blood pressure-lowering action of ramipril [20]. SEM is identified by bars.

Fig. 3.

In 25 persons with moderate hypercholesterolemia and untreated hypertension, pravastatin decreased systolic and diastolic blood pressure (−8 and −5 mmHg, both $p = 0.001$) when compared with placebo [17]. SEM is identified by bars.

Fig. 4.

(Left) In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA) trial, at baseline and study end (mean follow-up 3.3 years), the mean blood pressure of the 10,305 patients included did not differ between those allocated atorvastatin 10 mg and placebo. However, between 6 weeks and 18 months, those allocated statin had significantly lower blood pressure levels than those allocated placebo. Maximal differences were 1.1 mmHg systolic and 0.7 mmHg diastolic (both $p < 0.001$) [35]. (Right) Four hundred four patients in North America and Europe were randomized in a double-blind manner to receive 12 weeks of valsartan 160 mg ($n = 135$) or valsartan 160 mg added to simvastatin 20 ($n = 131$) or 80 mg ($n = 127$). All patients underwent 24 h ABP. ABP was reduced to a similar extent in all groups with no evidence for an additive effect with simvastatin on blood pressure [13].

Table 1

Effects of statins on blood pressure in patients

Patients	Authors	Statins	Delta SBP/Delta DBP	References
Hypertension (+)	Controlled hypertension			
	O'callaghan et al.	Pravastatin	No change	[11]
	Foss et al.	Pravastatin	+0.8/-0.8	[12]
	Rajagopalan et al.	Simvastatin 20 mg	+0.2	[13]
		Simvastatin 80 mg	-0.7	
	Ikeda et al.	Pravastatin 10 mg	-4.7 [*] /-0.7	[14]
	Uncontrolled hypertension			
	Straznicky et al.	Pravastatin 40 mg	+1/+1	[25]
	Fogari et al.	Atorvastatin 20 mg	-2.8/-3.8 [*]	[24]
	Koh et al.	Simvastatin 20 mg	-3/-3	[19]
	Borghi et al.	Prava or simvastatin	-4.7 [*] /-4.5 [*]	[15]
	Sposito et al.	Lova or pravastatin	-7 [*] /-4 [*]	[16]
	Glorioso et al.	Pravastatin	-8 [*] /-5 [*]	[17]
	Ferrier et al.	Atorvastatin 80mg	-6 [*] /-2 [*]	[5]
	Magen et al.	Atorvastatin 20mg	-13.7 [*] /-7.8 [*]	[21]
	Kanbay et al.	Atorvastatin 20mg	-5.1 [*] /-5.2 [*]	[22]
	Calvo et al.	Atorvastatin 10mg	-7.7 [*] /-4.9 [*]	[23]
	Terzoli et al.	Simva, prava, atorva	-5.7 [*] /-3.5 [*]	[32]
	Borghi et al.	Simvastatin	-12% [*] /-9% [*]	[33]
	Poulter and Sever	Atorvastatin 10mg	-1.1 [*] /-0.7 [*]	[35]
	Bak et al.	Pravastatin 20 mg	+1.9/+1.1	[26]
	Jenkins et al.	Lovastatin 20 mg	+5.2/-0.9	[27]
	Derosa et al.	Fluvastatin 80mg	-2/-2	[28]
	Shige et al.	Simvastatin 20-40 mg	+1/+1	[29]
	Lee et al.	Pravastatin 10-20 mg	-1/-1	[30]
	Tonolo et al.	Simvastatin 20 mg	0/+2	[31]
	Giannattasio et al.	Simvastatin 40 mg	+7.5/+6.0	[8]
Hypertension (-)	Kool et al.	Pravastatin 40 mg	+3/+1	[9]
	Baldassarre et al.	Pravastatin 20 mg	No change	[10]
	Koh et al.	Simvastatin 20 mg	+1/0	[20]
	Terzoli et al.	Simva, prava 10-20 mg	-0.7/-1	[32]
		Atorvastatin 5-10 mg		
	Borghi et al.	Simvastatin	-1%/-3%	[33]
	Leibovitz et al.	Atorvastatin 16mg	-6 [*] /-3 [*]	[4]
	Golomb et al.	Simvastatin 20 mg	-2.8 [*] /-2.7 [*]	[34]
		Pravastatin 40 mg	-2.5 [*] /-2.5 [*]	

* $p < 0.05$, statins vs. placebo or baseline. Controlled hypertension is defined by WHO criteria; SBP <140 mmHg and DBP <90 mmHg. % means percent change in SBP and DBP after 5 years of simvastatin from baseline SBP and DBP in the Brisighella Heart Study [33].